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Efficacy Of Old Antibiotics In The Treatment Of Neonatal Sepsis By Multidrug-Resistant Bacteria.

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ABSTRACT
Neonatal sepsis is a syndrome caused by a systemic infection in a newborn and is a significant cause of morbidity and mortality. The most common causative agents are bacteria, which vary according to the source of infection. There are two presentations of this pathology: Early Onset Sepsis (EOS) within the first 72 hours of life, or Late Onset Sepsis (LOS) after 4 to 7 days within the first 1 to 3 months of life1,2. The bacteria causing this syndrome are not exempt from the severe global problem currently being faced: Antibiotic Resistance (AMR). The presence of multi-drug resistant (MDR) bacteria is an issue that unfortunately has come to affect these patients, becoming a major therapeutic challenge. Therefore, this work presents an alternative treatment forthese cases, using antibiotics considered "old".

Keywords: *neonatal sepsis, multidrug-resistant organisms, antibiotics, treatment, colistin, fosfomycin*

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I. INTRODUCTION

Neonatal sepsis is a systemic infection that causes a variety of nonspecific signs and symptoms in a newborn. The causative agents of neonatal sepsis pathology statistically vary between developed and developing countries, but according to data from the American Neonatology Network, EOS are due to vertical transmission, with Gram-positive bacteria being more frequent, accounting for 62% (Streptococcus agalactiae 43%) and Gram-negative bacteria 37% (Escherichia coli 29%); while in LOS, 79% are Gram-positive (coagulase-negative Staphylococcus 57%) and 19% Gram-negative (Escherichia coli 7%), but the latter are secondary tonosocomial risk factors [3].

Currently, MDRs are a significant cause of mortality worldwide [4], establishing themselves as a threat that impacts indiscriminately, as a significant and increasing number of bacteria causing neonatal sepsis are resistant to multiple antibiotics, including the empirical pharmacological regimen used in neonatal sepsis, which consists of the use of a penicillin plus an aminoglycoside (usually ampicillin and gentamicin)[5]. In the presence of MDR, their use is in vain, and resistance has even been demonstrated to agents used as second-line treatment, such as cephalosporins and carbapenems, further complicating the management of this disease [6,7].

The fatality rate is higher in newborns with sepsis caused by MDR1, and there are multiple risk factors that predispose to this type of infection; horizontal transfer due to inadequate hospital infection control practices has been shown to be the main cause of this new obstacle [8].

II. METHODOLOGY

An observational, descriptive, and retrospective study was conducted. A bibliographic review was performed using the search engines Pubmed, EBSCO, and GoogleScholar, employing Medical Subjects Headings (MeSH) keywords "neonatal sepsis, colistin, antibiotic, antimicrobial resistance, therapy in neonatal sepsis" to gather articles with relevant information about the behavior of antibiotics in the management of neonatal sepsis.

Literature reviews, reports, and case series that contained information related to the objective of the work were included. A total of 841 works wereobtained, with 29 included in this review.

III. MULTIDRUG-RESISTANT ORGANISMS IN NEONATAL SEPSIS

AMR is an increasingly significant concern in the treatment of neonatal sepsis [5,9]; in various countries, especially those in development [6], neonatal sepsis caused by beta-lactamase-producing bacteria is one of the

most important causes of treatment failure and high mortality rate. These enzymes are more prevalent in Gram-negative bacteria, including Escherichia coli, Klebsiella species, Salmonella species, Shigella, Enterobacter species, Citrobacter species, Pseudomonas aeruginosa, Serratia marcescens, Providencia, Proteus mirabilis, and Morganella morganii, with Klebsiella pneumoniae, Acinetobacter baumannii [10], Escherichia coli, Enterobacter cloacae, Citrobacter diversus, Pseudomonas aeruginosa, Streptococcus pyogenes, and Staphylococcus aureus being prominent in this pathology [11,12]. Most MDR pathogens show high resistance to first-line drugs recommended by the WHO, such as ampicillin, gentamicin, and cefotaxime [13]. Due to the increased resistance, it is vitally important to have an alternative treatment for these organisms, and it is even perceived as necessary to develop a new first-line empirical treatment, as the current one is inefficient in the face of this problem [3].

IV. TREATMENT OF NEONATAL SEPSIS

The empirical treatment of neonatal sepsis is based on the evaluation of risk factors, clinical presentation, laboratory tests, and gestational age. This treatment should provide broad coverage against the most common microorganisms. Typically, a regimen of ampicillin plus an aminoglycoside is used, and even extended-spectrum cephalosporins are added in case of failure or other factors indicating an unexpected response to first-line treatment [14], a scenario currently highlighted by the increase in MDR.

In an era of growing antimicrobial resistance, there is a limited number of antibiotics available for treating multidrug-resistant infections in pediatric patients, particularly those caused by extended-spectrum β-lactamase-producing and carbapenem-resistant bacteria [15], This has led multiple scientific societies to raise alarms about the problem. This situation has necessitated the consideration of three possible actions: the use of new indications or dosing guidelines for antibiotics already used in sepsis treatment (tigecycline, meropenem), the introduction of "new" antibiotics (β-lactams, lipoglycopeptides, oxazolidinones), and the re-utilization of "old" antibiotics (colistin, fosfomycin)[16].

V. OLD ANTIBIOTICS IN THE TREATMENT OF NEONATAL SEPSIS

Old antibiotics have recently emerged as a promising treatment alternative, despite limited evidence regarding their safety profile and pharmacokinetics [15], because they retain the spectrum required for MDR and could be reused in the treatment of neonatal sepsis as it has been observed that many MDRs have regained susceptibility to these antibiotics.

Within this resurgence of old antibiotics, the use of colistin stands out due to the emergence of high resistance in Acinetobacter spp.[17] to almost all antibiotics, except colistin, as demonstrated in various studies [18], This has drawn the attention of the scientific community for its reuse in the treatment of neonatal sepsis. This polymyxin exerts its antibacterial action by displacing Mg^{2+} and Ca^{2+} ions from the lipopolysaccharide component of the outer membrane of Gram-negative bacteria, increasing permeability and causing loss of cellular content, leading to cell death [6].It is often the last active antibiotic against P. aeruginosa, A. baumannii, and other Gram-MDR, so its use should be reserved for these microorganisms.

On the other hand, fosfomycin, an antibiotic primarily used orally in the treatment of uncomplicated urinary infections, is defined as "critically important" by the World Health Organization due to its potential efficacy against multidrug-resistant bacteria, and is increasingly cited as a promising antibiotic to combat sepsis in an era of growing antimicrobial resistance [15]. La fosfomicina muestra ser una solución prometedora y asequible para combatir las bacterias MDR. Fosfomycin proves to be a promising and affordable solution to combat MDR bacteria. It inhibits phosphoenolpyruvate transferase, acting in the first stage of peptidoglycan synthesis, an earlier stage than most antibiotic classes in inhibiting the bacterial wall. Fosfomycin has a broad spectrum of activity against Gram-positive and Gram-negative organisms, including MDR organisms such as Methicillin-resistant Staphylococcus aureus (MRSA), Vancomycin-resistant Enterococcus faecium (VRE), and ESBL-resistant Enterobacteriaceae and CRE [15]. Differences in renal maturation in newborns influence the recommended dosing regimens; currently, there are divergent published oral dosing recommendations for children, although a current pharmacokinetic trial that has completed recruitment will soon provide clarity on dosing recommendations in neonates (https://clinicaltrials.gov/ct2/show/NCT03453177)[15]. Fosfomycin has the potential to develop rapid resistance if used in isolation, so its use should be explored as a clinical therapeutic option cautiously(and in combination with a second antibiotic) to preserve its susceptibility[19].

Tigecycline is an antibiotic that exerts bacteriostatic activity through the blockade of protein synthesis by binding to the 30S ribosomal subunit. It belongs to the group of glycylcyclines, is structurally similar to tetracyclines but with chemical modifications to prevent the most common resistance mechanisms. It is effective against a wide spectrum of Gram-positive and Gram-negative pathogens, anaerobes, and atypical bacteria, including MDR microbes such as methicillin-resistant, vancomycin-resistant Enterococcus spp., A. baumannii, and Gram-negative bacterial strains that produce ESBL and carbapenemases, with the exception of Pseudomonas spp [20]. The efficacy and safety of the drug cannot yet be defined due to the scarce reports on its

use; however, in some studies, such as that of Ipek et al., the results of all patients were favorable without serious adverse events [21], making it necessary to conduct more studies adjusted to the physiological characteristics of the newborn for the clarification of this drug. [22,23].

VI. NEW ANTIBIOTICS IN THE TREATMENTOF NEONATAL SEPSIS

The limited therapeutic options against drug-resistant Gram-negative bacteria have led to the development and study of several novel antibacterial agents, including combinations of β-lactam/β-lactamase inhibitors (BL-BLI). New antibiotics (e.g., ceftazidime-avibactam, meropenem-vaborbactam, imipenem/cilastatin-relebactam) appear to be promising based on adult study experience and, more recently, a very small but growing number of trials including newborns [20], However, although newly developed agents may have the "required" spectrum of activity, they are unlikely to be available in the near future due to licensing and cost limitations and the well-recognized delay in obtaining pediatric and neonatal licensing (which can be up to 10 years after adult licensing).

VII. RESULTS

Table 1 shows various latest-generation antibiotics used for the treatment of MDR Gram-negative bacteria [16]. In addition, the same table reveals that the spectrum covered by "old" antibiotics (colistin, tigecycline, and fosfomycin) is similar to that of the latest generation.

Colistin

Despite the nephrotoxicity caused by colistin, it is currently recommended to use higher doses than previously (4.5 MU/12 h, after a loading dose of 9 MU in critical patients with severe sepsis or shock). This is reaffirmed in 2 studies, reflected in Table 2, conducted by Ambreen & colleagues and Serafettin Tekgunduz & colleagues, which detail that the useof colistin against MDR bacteria achieved mycobacterial clearance in cultures when other broad-spectrum antibiotics did not (amikacin, meropenem)[18,24].

Antimicrobial	Family (route)	Dosage	Spectrum
Ceftaroline	Cephalosporin (I.V.)	600 mg/ 12 h	Enterobacteria (Non-ESBL) S. aureus (MSSA, MRSA) S. pneumoniae, S. pyogenes
Ceftobiprole	Cephalosporin (I.V.)	500 mg/ 8 h	Enterobacteria (Non-ESBL) P. aeruginosa, S. pneumoniae S. aureus (MSSA, MRSA)
Ceftolozane	Cephalosporin (I.V.)	2500 mg/ 8 h	Enterobacteria (ESBL) P. aeruginosa, B. fragilis
Oritavancin	Lipoglycopeptide (I.V.)	1200 mg/ DU	S. aureus (MSSA, MRSA, VISA, VRSA) Streptococcus, Enterococcus (VRE), ECN
Dalbavancin	Lipoglycopeptide (I.V.)	1000+500 mg/ 2 dosis (día 1 y 8)	S. aureus (MSSA, MRSA, VISA, VRSA)Streptococcus, Enterococcus, CoNS
Tedizolid	Oxazolidinone (I.V.)	200 mg/ 24 h (6días)	S. aureus (MSSA, MRSA), CoNS Streptococcus, Enterococcus, CoNS
Tigecyline	Glycylcycline (I.V.)	50 mg/ 12 h	A.baumannii, Enterobacteria (Carbapenemase-Producing and/or ESBL)
Colistin	Polymyxin E (I.V.)	10 mg/ día	Enterobacteriaceae producing ESBL and Carbapenemase P. aeruginosa, A.baumannii.
Fosfomycin	Phosphoric AcidDerivative	BGN: 4-6 g / 6-8 h BGP: 2 g / 6 h	GNB (Enterobacteriaceae producing Carbapenemase and ESBL), P. aeruginosa,GPB (MRSA, VISA, VRSA)

Use of Colistin in Neonatal Sepsis					
Studies	Patients	Bacteria	Side Effects	Associated Deaths	Comorbidities
Ambreen & cols	12	K. pneumoniae: 50% A. baumannii: 33.3% P. aeruginosa: 16.6%	- Reduction in serum levels of Na and K: 2 (16.6%) - Apnea: 4 (33,3%) - Seizure: 1 (8.3%)	6 (50%)	< 32 SDG (50%)
Serafettin Tekgunduz & cols	153	K. pneumonia: 50% A. baumannii: 22.5% Enterobacteria:18%	- Electrolyte imbalance: 18.3% - Seizures: 13.7% - Nephrotoxicity:5.2%	42 (27.5%)	~ 28. 3 SDG (27.5%)

Use of Fosfomycin in Neonatal Sepsis (Williams, 2020)				
Studies	Patients	Agents Used	Clinical Disease	Clinical Effectiveness
Baquero y cols.	6	Fosfomycin as Monotherapy	Septicemia	3 patients (50%)
	18	Fosfomycin + Gentamicin	Septicemia	16 patients (88%)
	2	Fosfomycin + Carbenicillin	Septicemia	2 patients (100%)
Rossignol y Regnier	21	Fosfomycin + Gentamicin/Tobramycin	Urosepsis	19 patients (90%)
Guillois y cols.	1	Fosfomycin + Vancomycin	Septicemia	1 patient (100%)
Gouyon y cols.	16	Fosfomycin + Cefotaxime	Septicemia	15 patients (93%)

Gestational age turned out to be one of the factors most associated with the success or failure of treatment with colistin. Our comparison with these studies shows that those patients with less than 32 weeks of gestational age (SDG) succumbed to the disease while those with more than 32 weeks of gestational age managed to survive. An adjustment in the colistin treatment dose may be needed for patients under 32 weeks of gestational age to achieve a successful outcome.

Various studies show that Colistin's susceptibility to Gram-negative bacilli (BGN) is high [25, 26], as in the study shown by Ece & colleagues, 2014, where the susceptibility of colistin was 100%. Somily & colleagues, 2019, demonstrate that colistin has greater susceptibility than carbapenems, showing susceptibilities greater than 93%.

Fosfomycin

The study published by Williams in 2020 compares various studies in which the use of fosfomycin in 64 pediatric patients with sepsis stands out. It is evident that along with the adjuvance of other medications, the outcome is favorable. Its low international use since its discovery has led to preserved susceptibility to a large number of organisms 15, and due to its high tissue penetration, it is used for the treatment of urinary infections in both the U.S. and Europe. Its susceptibility to both Gram-positive and Gram-negative bacteria is high, with an average of around 80% [27].

VIII. CONCLUSIÓN

Currently, AMR threatens the well-being of the most vulnerable population, and the absence of therapeutic alternatives against MDR, mainly against beta-lactamase-producing bacteria, has prompted the need to find other treatments. It has been found that "older" antibiotics (colistin, fosfomycin, tigecycline) are effective in managing infections caused by these bacteria. The treatment of neonatal sepsis due to MDR is complex and challenging, which is why close collaboration between scientific societies, health authorities, research laboratories, and the pharmaceutical industry is now more necessary than ever to face the challenge of this new "post-antibiotic" and not only prioritize treatment but also focus on prevention, through good infection control practices [28,29].